CLAIMS

We claim:

1. An isolated nucleic acid having a nucleotide sequence selected from the group consisting of:

(a) at least 10 consecutive nucleotides of SEQ ID NO: 1;

(b) at least 12 consecutive nucleotides of SEQ ID NO: 1;

(c) at least 14 consecutive nucleotides of SEQ ID NO: 1;

(d) at least 16 consecutive nucleotides of SEQ ID NO: 1;

(e) at least 18 consecutive nucleotides of SEQ ID NO: 1; and

(f) a sequence complementary to any one of the sequences of (a) –(e).

2. An isolated nucleic acid having a nucleotide sequence selected from the group consisting of:

(a) at least 10 consecutive nucleotides of SEQ ID NO: 3;

(b) at least 12 consecutive nucleotides of SEQ ID NO: 3;

(c) at least 14 consecutive nucleotides of SEQ ID NO: 3;

(d) at least 16 consecutive nucleotides of SEQ ID NO: 3;

(e) at least 18 consecutive nucleotides of SEQ ID NO: 3; and

(f) a sequence complementary to any one of the sequences of (a) –(e).

3. An isolated nucleic acid having a nucleotide sequence selected from the group consisting of:

(a) a sequence encoding a CatSper1 protein;

(b) a sequence encoding at least a transmembrane domain of a CatSper1 protein;

(c) a sequence encoding at least an extracellular loop of a CatSper1 protein;

(d) a sequence encoding at least a pore region of a CatSper1 protein;

(e) a sequence encoding at least an epitope of a CatSper1 protein having high predicted antigenicity; and

(f) a sequence complementary to any one of the sequences of (a)–(e).

4. An isolated nucleic acid as in claim 3 selected from the group consisting of:

(a) SEQ ID NO: 1;

(b) SEQ ID NO: 3;

(c) a sequence encoding a polypeptide comprising residues 447-468, 481-502, 516-533, 542-563, 583-604 or 649-670 of SEQ ID NO: 2;

(d) a sequence encoding a polypeptide comprising residues 351-372, 385-406, 419-438, 448-469, 489-510, or 555-576 of SEQ ID NO: 4;

(e) a sequence encoding a polypeptide comprising residues 469-480, 534-541, or 605-648 of SEQ ID NO: 2;

(f) a sequence encoding a polypeptide comprising residues 373-384, 439-448, and 511-554 of SEQ ID NO 4;

(g) a sequence encoding a polypeptide comprising residues 616-635 of SEQ ID NO: 2;

(h) a sequence encoding a polypeptide comprising residues approximately residues 522-541 of SEQ ID NO: 4;

(i) a sequence encoding a polypeptide comprising residues 2-34, 52-70, 108-130, 264-305, 387-417, or 606-614 of SEQ ID NO: 2;

(j) a sequence encoding a polypeptide comprising residues 2-40, 120-148, 160-200, or 512-520 of SEQ ID NO: 4; and

(k) a sequence complementary to any one of the sequences of (a)–(j).

5. An isolated nucleic acid encoding a polypeptide having at least 80% amino acid sequence identity with a polypeptide selected from the group consisting of:

(a) a CatSper1 protein;

(b) at least a transmembrane domain of a CatSper1 protein;

(c) at least an extracellular loop of a CatSper1 protein; and

(d) at least a pore region of a CatSper1 protein.

6. An isolated nucleic acid encoding a polypeptide having at least 80% amino acid sequence identity with a CatSper1 protein and having CatSper1 activity in a cell capable of expressing CatSper1 activity.

7. An isolated nucleic acid comprising

a regulatory element having at least 80% nucleotide sequence identity to at least 100 consecutive nucleotides selected from SEQ ID NO: 5;

wherein said regulatory element is capable of promoting transcription of a coding sequence operably joined thereto in a mammalian cell in which a CatSper1 gene can be expressed.

8. An isolated nucleic acid comprising a nucleotide sequence that hybridizes to at least a portion of a nucleic acid of SEQ ID NO: 1 or SEQ ID NO: 3 under conditions including a wash step of 1.0 x SSC at 65°C.

9. An isolated nucleic acid as in claim 8 wherein said nucleic acid encodes a polypeptide having CatSper1 activity.

10. A nucleic acid comprising:

(i) a nucleotide sequence encoding a polypeptide having CatSper1 activity, wherein said nucleic acid hybridizes to at least a portion of a nucleic acid of SEQ ID NO: 1 or SEQ ID NO: 3 under conditions including a wash step of 1.0 x SSC at 65°C; and

(ii) a heterologous regulatory region operably joined to said sequence such that said sequence is expressed.

11. A nucleic acid comprising:

(i) a nucleotide sequence encoding a polypeptide having at least 80 percent amino acid sequence identity with an amino acid sequence of SEQ ID NO: 2 or 4; and

(ii) a heterologous regulatory region operably joined to said sequence such that said sequence is expressed.

12. A kit for detecting at least a portion of a CatSper1 nucleic acid comprising an isolated nucleic acid of any one of claims 1-7 and a means for detecting said isolated nucleic acid.

13. A kit as in claim 12 wherein said means for detecting said isolated nucleic acid comprises a detectable label bound thereto.

14. A kit as in claim 12 wherein said means for detecting said isolated nucleic acid comprises a labeled secondary nucleic acid which specifically hybridizes to said isolated nucleic acid.

15. A vector comprising an isolated nucleic acid of any one of claims 1-11.

16. A vector comprising a genetic construct capable of expressing a nucleic acid of any one of claims 3-11.

17. A vector as in claim 16 wherein said nucleic acid is operably joined to an exogenous regulatory region.

18. A vector as in claim 16 wherein said nucleic is operably joined to heterologous coding sequences to form a fusion vector.

19. A vector comprising an isolated nucleic acid of any one of claims 3-11.

20. A vector comprising an isolated nucleic acid of any one of claims 3-11 operably joined to a reporter gene.

21. A cell transformed with a nucleic acid of any one of claims 3-11.

22. A cell transformed with a genetic construct capable of expressing a nucleic acid of any one of claims 3-11.

23. A cell as in claim 22 wherein said nucleic is operably joined to heterologous coding sequences to encode a fusion protein.

24. A cell as in claim 22 wherein said cell is selected from the group consisting of bacterial cells, yeast cells, insect cells, nematode cells, amphibian cells, rodent cells, and human cells.

25. A cell as in claim 22 wherein said cell is selected from the group consisting of mammalian somatic cells, fetal cells, embryonic stem cells, zygotes, gametes, germ line cells and transgenic animal cells.

26. A non-human transgenic animal, wherein a genetic construct has introduced a modification into a genome of said animal, or an ancestor thereof, and wherein said modification is selected from the group consisting of insertion of a nucleic acid encoding at least a fragment of a CatSper1 protein, inactivation of an endogenous CatSper1 gene, and insertion by homologous recombination of a reporter gene operably joined to CatSper1 regulatory elements.

27. An animal as in claim 26 wherein said modification is insertion of a nucleic acid encoding a polypeptide selected from the group consisting of a CatSper1 protein, at least a transmembrane domain of a CatSper1 protein, at least an extracellular loop of a CatSper1 protein, at least a pore region of a CatSper1 protein, and at least an epitope of a CatSper1 protein having high predicted antigenicity.

28. An animal as in claim 26 wherein said animal is selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbit, dogs, cats, goats, sheep, pigs, and non-human primates.

29. A substantially pure protein preparation comprising a polypeptide selected from the group consisting of:

(a) a CatSper1 protein;

(b) at least a transmembrane domain of a CatSper1 protein;

(c) at least an extracellular loop of a CatSper1 protein;

(d) at least a pore region of a CatSper1 protein; and

(e) at least an epitope of a CatSper1 protein having high predicted antigenicity.

30. A substantially pure protein preparation as in claim 29 wherein said polypeptide is selected from the group consisting of:

(a) SEQ ID NO: 2;

(b) SEQ ID NO: 4;

(c) residues 447-468, 481-502, 516-533, 542-563, 583-604 or 649-670 of SEQ ID NO: 2;

(d) residues 351-372, 385-406, 419-438, 448-469, 489-510, or 555-576 of SEQ ID NO: 4;

(e) residues 469-480, 534-541, or 605-648 of SEQ ID NO: 2;

(f) residues 373-384, 439-448, and 511-554 of SEQ ID NO 4;

(g) residues 616-635 of SEQ ID NO: 2;

(h) residues 522-541 of SEQ ID NO: 4;

(i) residues 2-34, 52-70, 108-130, 264-305, 387-417, or 606-614 of SEQ ID NO: 2; and

(j) residues 2-40, 120-148, 160-200, or 512-520 of SEQ ID NO: 4.

31. A substantially pure protein preparation comprising a polypeptide having at least 80% amino acid sequence identity with a polypeptide selected from the group consisting of:

(a) a CatSper1 protein;

(b) at least a transmembrane domain of a CatSper1 protein;

(c) at least an extracellular loop of a CatSper1 protein; and

(d) at least a pore region of a CatSper1 protein.

32. A substantially pure protein preparation comprising a polypeptide having at least 80% amino acid sequence identity with a CatSper1 protein and having CatSper1 activity in a cell capable of expressing CatSper1 activity.

33. A substantially pure antibody preparation comprising an antibody raised against a CatSper1 epitope.

34. A substantially pure antibody preparation as in claim 33 wherein said epitope has high predicted antigenicity.

35. A substantially pure antibody preparation as in claim 33 wherein said epitope comprises an amino acid sequence within the an amino acid sequence selected from the group consisting of residues 2-34, 52-70, 108-130, 264-305, 387-417, and 606-

614 of SEQ ID NO: 2, and residues 2-40, 120-148, 160-200, or 512-520 of SEQ ID NO: 4.

36. A substantially pure antibody preparation as in any one of claims 33-35 wherein said antibody is a monoclonal antibody.

37. A substantially pure antibody preparation as in any one of claims 33-35 wherein said antibody is an antibody fragment selected from the group consisting of an Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment (scFv).

38. A kit for detecting at least an epitope of a CatSper1 protein comprising an anti-CatSper1 antibody of any one of claims 33-37 and a means for detecting said antibody.

39. A kit as in claim 38 wherein said means for detecting said anti-CatSper1 antibody comprises a detectable label bound thereto.

40. A kit as in claim 38 wherein said means for detecting said anti-CatSper1 antibody comprises a labeled secondary antibody which specifically binds to said anti-CatSper1 antibody.

41. A method of identifying a potential modulator of CatSper1 activity comprising:

contacting a candidate compound with a cell expressing a CatSper1 protein;

measuring an indicator of CatSper1 activity in said cell;

determining whether said candidate compound caused an increase or decrease in said indicator relative to a reference level; and

identifying said candidate compound as a potential modulator of CatSper1 activity if said increase or decrease is significant.

42. A method as in claim 41 wherein said indicator is an indicator of the level of mRNA encoding said CatSper1 protein.

43. A method as in claim 41 wherein said indicator is an indicator of the level of CatSper1 protein.

44. A method as in claim 41 wherein said indicator is an indicator of cation flux across a membrane of said cell.

45. A method as in claim 41 wherein said indicator is an indicator of whole cell or channel currents of said cell.

46. A method as in any one of claims 41-45 wherein said cell has been transformed with a genetic construct capable of expressing a CatSper1 protein.

47. A method as in claim 41 wherein said cell is a mature sperm cell and said indicator is a measure of sperm motility.

48. A method of identifying a potential modulator of CatSper1 activity comprising:

contacting under physiological conditions a candidate compound with CatSper1 moiety comprising at least a structural domain of a CatSper1 protein;

measuring binding, if any, between said candidate compound and said CatSper1 moiety;

identifying said candidate compound as a potential modulator of CatSper1 activity if said binding is significant.

49. A method as in claim 48 wherein said CatSper1 moiety is a polypeptide selected from the group consisting of:

(a) a CatSper1 protein;

(b) at least a transmembrane domain of a CatSper1 protein;

(c) at least an extracellular loop of a CatSper1 protein; and

(d) at least a pore region of a CatSper1 protein.

50. A method of decreasing the fertility of a male subject comprising:

administering to said male a compound which decreases CatSper1 activity.

51. A method of causing reversible infertility in a male subject comprising:
administering to said male a compound which decreases CatSper1 activity.

52. A method of contraception comprising:
administering to a male subject a compound which decreases CatSper1 activity.

53. A method of contraception comprising:
administering to a female subject a compound which decreases CatSper1 activity.

54. A method as in any one of claims 50-53 wherein said compound is in a formulation selected from the group consisting of an injection, a transdermal patch, a bioerodable implant, a lubricant, a moisturizer, a foam, a jelly, and a sponge.

55. A method of contraception as in claim 53 wherein:
said female subject is a mammal and said compound is administered into at least one of the vagina, uterus and fallopian tubes of said female.

56. A method as in any one of claims 50-53 wherein said compound is selected from the group consisting of a nucleic acid which is antisense to at least a portion of a CatSper1 gene and an antibody to a CatSper1 protein.

57. A method as in claim 56 wherein said compound is an antibody fragment selected from the group consisting of an Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and an scFv fragment.

58. A method as in any one of claims 50-53 wherein said subject is a mammal.

59. A method as in claim 58 wherein said mammal is selected from the group consisting of humans, dogs, cats, cows, sheep, horses, mice, rats, raccoons, and gophers.

60. A method as in claim 58 wherein said subject is selected from the group consisting of a fish, an amphibian and an insect.

61. Use of a compound which decreases CatSper1 activity in the preparation of a medicament for decreasing the fertility of a male subject.

62. Use of a compound which decreases CatSper1 activity in the preparation of a medicament for causing reversible infertility in a male subject.

63. Use of a compound which decreases CatSper1 activity in the preparation of a contraceptive for administration to a male.

64. Use of a compound which decreases CatSper1 activity in the preparation of a contraceptive for administration to a female.

65. A use as in any one of claims 61-64 wherein said compound is in a formulation selected from the group consisting of an injection, a transdermal patch, a bioerodable implant, a lubricant, a moisturizer, a foam, a jelly, and a sponge.

66. A use as in claim 64 wherein:

said female subject is a mammal and said compound is administered into at least one of the vagina, uterus and fallopian tubes of said female.

67. A use as in any one of claims 61-64 wherein said compound is selected from the group consisting of a nucleic acid which is antisense to at least a portion of a CatSper1 gene and an antibody to a CatSper1 protein.

68. A use as in claim 67 wherein said compound is an antibody fragment selected from the group consisting of an Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and an scFv fragment.

69. A use as in any one of claims 61-64 wherein said subject is a mammal.

70. A use as in claim 69 wherein said mammal is selected from the group consisting of humans, dogs, cats, cows, sheep, horses, mice, rats, raccoons, and gophers.

71. A use as in claim 69 wherein said subject is selected from the group consisting of a fish, an amphibian and an insect.

72. A contraceptive preparation comprising a compound which decreases CatSper1 activity.

73. A preparation as in claims 72 wherein said compound is selected from the group consisting of a nucleic acid which is antisense to at least a portion of a CatSper1 gene and an antibody to a CatSper1 protein.

74. A preparation as in claim 72 wherein said preparation is in a formulation selected from the group consisting of an injection, a transdermal patch, a bioerodable implant, a lubricant, a moisturizer, a foam, a jelly, and a sponge.

75. A method of diagnosing a CatSper1-related disorder in a mammal comprising determining the presence or absence of a mutation in a CatSper1 gene.

76. A method as in claim 75 wherein said method comprises:

determining at least a portion of a CatSper1 gene sequence and comparing said determined sequence to a reference sequence;

wherein the presence or absence of differences between said determined sequence and said reference sequence indicate the presence or absence of mutations in said CatSper1 gene.

77. A method of diagnosing a CatSper1-related disorder comprising determining the presence or absence of a mutation in a CatSper1 protein.

78. A method as in claim 77 wherein said method comprises:

determining at least a portion of a CatSper1 protein sequence and comparing said determined sequence to a reference sequence;

wherein the presence or absence of differences between said determined sequence and said reference sequence indicate the presence or absence of mutations in said CatSper1 gene.

79. A method as in claim 78 wherein said determination comprises contacting at least a fragment of said CatSper1 protein with an antibody known to bind to a CatSper1 protein in which a mutation is known to be present or absent and detecting binding between said antibody and said fragment of said CatSper1 protein.

80. A method of diagnosing a CatSper1-related disorder in a mammal comprising
measuring an indicator of CatSper1 activity in said cell; and
comparing said measured indicator to a reference level.

81. A method as in claim 80 wherein said indicator is an indicator of the level of mRNA encoding said CatSper1 protein.

82. A method as in claim 80 wherein said indicator is an indicator of the level of CatSper1 protein.

83. A method as in claim 80 wherein said indicator is an indicator of cation flux across a membrane of said cell.

84. A method as in claim 80 wherein said indicator is an indicator of whole cell or channel currents of said cell.

85. A method as in any one of claims 75-84 wherein said disorder is CatSper1-related infertility.

86. A method of genotyping a subject with respect to a CatSper1 gene comprising:
determining at least a portion of a CatSper1 gene sequence and comparing said determined sequence to a reference sequence;
wherein the presence or absence of differences between said determined sequence and said reference sequence indicate the presence or absence of a genotype corresponding to said reference sequence.

87. A method of genotyping a subject with respect to a CatSper1 gene comprising:

determining at least a portion of a CatSper1 protein sequence and comparing said determined sequence to a reference sequence;

wherein the presence or absence of differences between said determined sequence and said reference sequence indicate the presence or absence of a genotype corresponding to said reference sequence.

88. A method as in claim 87 wherein said determination comprises contacting at least a fragment of said CatSper1 protein with an antibody known to bind to a CatSper1 protein comprising said reference sequence and detecting binding between said antibody and said fragment of said CatSper1 protein.

89. A method of *in vitro* fertilization by sperm having decreased CatSper1 activity comprising:

removing a zona pellucida from at least one ovum;

contacting said ovum with at least one of said sperm; and

allowing said sperm to fertilize said ovum.

90. A method of *in vitro* fertilization by sperm having decreased motility comprising:

removing a zona pellucida from at least one ovum;

contacting said ovum with at least one of said sperm; and

allowing said sperm to fertilize said ovum.

91. A method of *in vitro* fertilization by sperm having decreased ability to penetrate a zona pellucida comprising:

removing a zona pellucida from at least one ovum;

contacting said ovum with at least one of said sperm; and

allowing said sperm to fertilize said ovum.

92. A method of treating a subject characterized by infertility due to decreased CatSper1 activity comprising:

transforming sperm or sperm progenitors of said subject with a genetic construct capable of expressing a CatSper1 protein; and

using transformed sperm of said subject to fertilize an ovum.

93. A method of treating a subject characterized by infertility due to decreased CatSper1 activity comprising:

administering a CatSper1 protein to sperm or sperm progenitors of said subject, whereby said protein provides CatSper1 activity in said sperm or spermatids; and

using sperm bearing said administered CatSper1 protein to fertilize an ovum.

94. A method of diagnosing an anti-CatSper1 antibody-mediated infertility caused by anti-CatSper1 antibodies present in a female urogenital tract comprising:

obtaining a sample of antibodies present in a female urogenital tract;

contacting said sample of antibodies with at least a fragment of a CatSper1 protein; and

detecting binding between said sample of antibodies and said fragment of a CatSper1 protein.

95. A method as in claim 94 wherein said CatSper1 fragment comprises a CatSper1 epitopes having high predicted antigenicity.

96. A method as in claim 95 wherein said epitope is included within a sequence selected from the group consisting of residues 2-34, 52-70, 108-130, 264-305, 387-417, and 606-614 of SEQ ID NO: 2, and residues 2-40, 120-148, 160-200, and 512-520 of SEQ ID NO: 4.

97. A method of treating an anti-CatSper1 antibody-mediated infertility caused by anti-CatSper1 antibodies present in a female urogenital tract, comprising:

administering into said urogenital tract an agent which specifically binds to said anti-CatSper1 antibodies in an amount effective to inhibit binding between said anti-CatSper1 antibodies and a CatSper1 protein present on sperm in said urogenital tract.

98. A method as in claim 97 wherein said agent comprises at least fragment of a CatSper1 protein including an epitope having high predicted antigenicity.

99. A method as in claim 98 wherein said epitope is included within a sequence selected from the group consisting of residues 2-34, 52-70, 108-130, 264-305, 387-417, and 606-614 of SEQ ID NO: 2, and residues 2-40, 120-148, 160-200, and 512-520 of SEQ ID NO: 4.

100. A method as in claim 98 wherein said agent comprises an anti-idiotypic antibody against said anti-CatSper1 antibodies.

101. A method of conducting a drug discovery business comprising:

(a) identifying, by the assay of claim 41, one or more agents which antagonize CatSper1 activity;

(b) determining if an agent identified in step (a), or an analog thereof, inhibits at least one of sperm motility or egg penetrance;

(c) conducting therapeutic profiling of an agent identified as an inhibitor in step (b) for efficacy and toxicity in one or more animal models; and

(d) formulating a pharmaceutical preparation including one or more agents identified in step (c) as having an acceptable therapeutic profile.

102. The method of claim 101, further including the step of establishing a system for distributing the pharmaceutical preparation for sale, and optionally including establishing a sales group for marketing the pharmaceutical preparation.

103. A method of conducting a drug discovery business comprising:

(a) identifying, by the assay of claim 41, one or more agents which agonize CatSper1 activity;

(b) determining if an agent identified in step (a), or an analog thereof, increases at least one of sperm motility or egg penetrance;

(c) conducting therapeutic profiling of an agent identified as an agonist in step (b) for efficacy and toxicity in one or more animal models; and

(d) formulating a pharmaceutical preparation including one or more agents identified in step (c) as having an acceptable therapeutic profile;

104. The method of claim 101, further including the step of establishing a system for distributing the pharmaceutical preparation for sale, and optionally including establishing a sales group for marketing the pharmaceutical preparation.

105. The method of claim 103, wherein step (a) comprises identifying one or more agents which agonize the activity of wild type CatSper1.

106. The method of claim 103, wherein step (a) comprises identifying one or more agents which agonize the activity of a CatSper1 protein containing one or more mutations.

107. A method of conducting a reproductive medicine business comprising:
(a) examining a sperm sample from a male patient, wherein said patient is experiencing a fertility problem;
(b) determining if said sperm are characterized by at least one of a decrease in motility or a decrease in egg penetrance;
(c) performing *in vitro* analysis to determine the efficacy of a CatSper1 agonist in increasing at least one of sperm motility or egg penetrance;
(d) establishing a treatment regimen comprising administering an amount of a CatSper1 agonist effective to increase at least one of sperm motility or egg penetrance in said male.

108. The method of claim 107, further including a step wherein said male is monitored by a physician to evaluate improvement in fertility.

109. The method of claim 107, further including a step of billing the patient or the patient's health care provider.

110. A method of conducting a contraceptive medicine business comprising:
(a) providing a pharmaceutical preparation discovered in claim X01, wherein said preparation inhibits the activity of CatSper1;

(b) providing instructions to physicians and health care providers for the administration of an amount of said pharmaceutical preparation effective to inhibit the activity of CatSper1, wherein said effective amount is sufficient to prevent pregnancy.

111. The method of claim 110, further including the step of establishing a system for distributing the pharmaceutical preparation for sale, and optionally including establishing a sales group for marketing the pharmaceutical preparation.